inhibited, whereas RNA and protein synthesis continued at normal levels. All of these results suggested that reovirus RNA may possess distinguishing structural features. The anomalous staining with acridine orange raised the possibility that reovirus RNA, unlike any other known RNA, may be double-stranded. Results of physical-chemical studies have provided strong evidence in support of this view. Purified reovirus contains 14.7% RNA, but no DNA. The sedimentation coefficient of the virus, $s_{20} = 630$ S, is consistent with a minimal particle weight of 70×10^6 and a minimal complement of RNA of 10×10^6 per particle. The base ratios are approximately complementary. The mole percentage of G + C is 40.7. Reovirus RNA melts sharply in a narrow temperature range and reacts minimally with formaldehyde at 30° C. Thus, reovirus RNA appears to have a secondary structure similar to that of DNA. Both in this respect and also with respect to the large amount of genetic material in the virus particle, reovirus is unique among RNA viruses.

Correlation between Pathology and Function in Experimental Pyelonephritis: Studies on Concentrating Ability. H. C. GONICK, R. Y. FOOS, M. E. RUBINI, AND L. B. GUZE,* Los Angeles, Calif.

The early appearance of a concentrating defect is a distinguishing feature of human pyelonephritis. Current concepts suggest the following possible mechanisms: *1)* alteration of the tonicity of the medullary interstitium (by changes in medullary blood flow, distal reabsorption of sodium and urea, or increased deposition of collagenous protein); *2)* diminished responsiveness of the collecting ducts to circulating ADH; and *3)* increased solute flow per nephron occasioned by a reduction in total nephron mass. The development of an experimental model of pyelonephritis in the rat has permitted a systematic study of the progression of histological and chemical changes in the kidney as they relate to urinary concentration. Concentrating ability was evaluated by maximal U_{osm} and $T^c_{H_2O}$ (over a wide range of solute flow) at weekly intervals after the single injection of 10^7 *Enterococci* and at 12 weeks after repetitive injections. Reduction in maximal U_{osm} was seen as early as 1 week after infection ($1{,}369 \pm 448$ against $2{,}338 \pm 358$ mOsm per L); a further significant reduction was noted in the 12-week repetitive group (800 ± 146 mOsm per L). Diminution in $T^c_{H_2O}$, however, was not apparent until 12 weeks. Creatinine and para-aminohippurate clearances in the 12-week group did not differ significantly from normal controls. Analysis of papillae from the repetitively infected group showed no change in tissue water content or urea content as compared with normal (85.5 ± 3.1 against 85.0 ± 4.4% total wt and $.35 \pm .05$ against $.36 \pm .10$ moles per kg H_2O, respectively). Thus, a reduction in nephron mass could not account for the concentrating abnormality; decreased interstitial tonicity appears unlikely. The defect is most directly attributable to a diminished responsiveness of the abnormal collecting duct to antidiuretic hormone. This conclusion is supported by the pathological findings of structural alterations in collecting ducts without significant deposition of interstitial collagen or loss of glomeruli.

Substrate Balance in Fasting: The Response of Plasma Free Fatty Acid to Minute Changes in Plasma Glucose. CHARLES J. GOODNER AND J. THOMAS DOWLING, Seattle, Wash. (introduced by Robert G. Petersdorf).

It is well known that glucose and insulin inhibit the release of FFA from adipose tissue. The unexpected finding that in fasting normal subjects a single iv injection of 500 mg glucose is followed by prompt and sustained lowering of FFA (−20% in 10 minutes, −30% in 20 minutes, −14% in 40 minutes, and −10% in 50 minutes) suggested that the plasma concentration of glucose critically controlled release of FFA. The "catalytic" nature of this effect is apparent from the estimates that 500 mg glucose (2 Kcal) equals only 1 to 2 minutes of basal caloric requirement, or 3 minutes of substitution for hepatic glucose production, whereas FFA metabolism was altered for over 50 minutes. Several observations suggest that this effect is not mediated through acute secretion of insulin. *1)* The increment in arterial glucose (+2.8 mg per 100 ml at 10 minutes, +1.5 mg per 100 ml at 30 minutes, and 1.0 mg per 100 ml at 60 minutes) was probably too small to stimulate insulin release. *2)* With constant infusion of glucose at low rate (8 to 100 mg per minute), while FFA fell promptly, plasma glucose rose progressively during the first 60 to 80 minutes. Compensation, characterized by a simultaneous fall in glucose and rise in FFA back to control levels, was delayed until the second hour of infusion. Such a sequence suggests that insulin did not initiate or perpetuate the depression of FFA. *3)* Both treated and untreated adult diabetic subjects responded to 500 mg glucose regardless of the fasting glucose level (110 to 250 mg per 100 ml). *4)* Fructose (500 mg) produced the same response in normal subjects. The marked sensitivity of FFA metabolism to small increments in plasma glucose suggests that the fasting level of FFA is directly set by the availability of hexose at some responsive site. Whether this site is the fat cell per se, or a central locus controlling sympathetic tone or release of lipolytic hormones remains to be determined.

Cardiac Manifestations of Disturbed Intermediary Metabolism in Cholera. ROBERT S. GORDON, JR.,* WILLIAM B. GREENOUGH III, ABRAM S. BENENSON, KAMALUDDIN AHMAD, AND IRWIN H. ROSENBERG, Dacca, East Pakistan.

Certain cases of cholera show left heart failure, and develop pulmonary edema, remaining hypotensive, when fluid is replaced. Two cases with intractable failure died and were autopsied. Electrocardiographic changes, evolving toward normal during convalescence, are seen in nearly all cases. Flattening of T waves with normal QRS voltage is common; ST segment deviation occurs

in the more severe cases. Restoration of blood volume, replacement of calcium, potassium, and magnesium, and correction of acidosis fail to restore the electrocardiogram to normal. Administration of glucose exaggerates the ST segment deviation, and produces nausea, mental depression, and abnormal elevation of blood pyruvate. It is postulated that toxic products of *V. cholerae* give rise to a general metabolic disorder that is not merely a consequence of loss of fluid and electrolytes. The addition of tetracycline and water-soluble vitamins to the usual fluid replacement regimen in the treatment of cholera is beneficial. Although neurological examination, erythrocyte transketolase studies, and urinary thiamine excretion data have failed to demonstrate preexisting beriberi, thiamine is felt to be important in therapy on the basis of cardiac findings and elevation of blood pyruvate. Subclinical ascorbic acid deficiency exists in the area during the season of peak cholera incidence, and low blood levels of this vitamin, but no frank scurvy, have been found in cholera patients. Electrocardiographic improvement has followed treatment with large doses of ascorbic acid alone. Further studies are being undertaken that are designed to elucidate the role of nutritional factors in the etiology and pathologic physiology of cholera.

Kinetic Analysis of the Initial Distribution and Rate of Uptake of Sulfobromophthalein (BSP) in the Liver. C. A. Goresky, Montreal, Canada (introduced by Francis P. Chinard).

Multiple-indicator dilution curves have been obtained after the simultaneous injection of labeled red cells, labeled albumin, and BSP into the portal circulation of the dog. Recoveries are expressed as fractions of the amount injected per milliliter of hepatic venous blood. The albumin curve is displaced relative to the red cell curve, and shows a lower peak concentration and a delayed transit. The dilution curve for BSP, bound to albumin, exhibits an upstroke that parallels the labeled albumin curve, a slightly lower peak, and a more rapid exponential decay. The difference between the albumin and BSP curves is largest for small doses, smallest for large doses. The data have been analyzed by means of a flow-limited, linear, two-compartment model system in which the rate of BSP removal from the second compartment is assumed proportional to the product of the concentration and the volume of the extravascular space. Theoretical consideration of this model leads to a method of graphical analysis of the group of indicator dilution curves that permits the *direct* estimation of both the volume of extravascular space accessible to BSP and the rate constant for removal. In this instance, the BSP is found to be distributed into an extravascular space equivalent in volume to that accessible to the diffusible reference substance, albumin. The rate constant for BSP removal diminishes with increasing dose, indicating saturation of transport at larger doses. From the initial rates of removal (rate constant × dose) as a function of dose, an affinity constant and maximal transport capacity were calculated for the system transporting BSP into the parenchymal cells. These studies show this maximal transport capacity to be many times the steady-state maximum for transport from blood to bile. This excess transport capacity results in relatively rapid equilibration between cellular contents and plasma.

Inferential Evidence for the Fenn Effect in the Human Heart. Richard Gorlin,* Peter M. Yurchak, Ellis L. Rolett, William C. Elliott, and Lawrence S. Cohen, Boston, Mass.

A correlation has been shown in skeletal muscle, not only between energy cost (qO_2) and tension, but also between energy and fiber shortening distance (Fenn). Although cardiac tension is a function of both radius and pressure, the pressure-time component alone usually correlates with qO_2. This may be fortuitous because other mechanical factors, i.e., radius and fiber shortening, change quantitatively so much less than pressure-time. The catecholamines that change both heart size and fiber shortening have permitted examination of energy cost coincident with fiber shortening. Seven subjects were studied by left ventricular (LV) and coronary sinus catheterization, before and during norepinephrine and isoproterenol infusion, with measurement of qO_2 per 100 g per beat and LV volumes (thermal dilution), and calculation of force-time and circumferential shortening per beat. In three subjects, qO_2 with catechols directly paralleled force-time; shortening was unchanged. In the others, with increased shortening "excess qO_2" could be calculated above that equatable to force-time. Supporting evidence was obtained in 30 subjects with no volume studies. In 10 in whom stroke volume did not change and LV end-diastolic pressure rose or remained unchanged, qO_2 rose *pari passu* with increase in pressure-time. In the other 20, a correlation of 0.59 ± 0.22 existed between change in stroke volume and qO_2 in excess of that predicted from pressure-time. End-diastolic pressure decreased in 13 of 19 observations. The combination of end-diastolic volume decrease and stroke volume increase represents even greater increase in shortening distance. Thus, in this larger series, a portion of energy again appeared related to shortening. These studies suggest that extensive fiber shortening can have an energy cost of its own. Thus, during catechol exhibition, cardiac qO_2 increased out of proportion to force only when fiber shortening was increased. In no instance was qO_2 "wasted" by catechols, and energy could be related to the various induced changes in mechanical performance.

Circulatory Consequences of Changes in Cardiac Rhythm Produced in Patients by Transthoracic Direct-Current Shock. John S. Graettinger, Richard A. Carleton, and Joseph J. Muenster, Chicago, Ill. (introduced by Theodore B. Schwartz).

Patients with ectopic atrial rhythms have been studied before and after conversion to sinus rhythm by means of direct-current shock across the closed chest. Cardiac out-